REMARKS

I. Status of the Claims

Claims 29-60 are pending in the application. Claims 52-57, 59 and 60 are withdrawn pursuant to a restriction requirement and are hereby canceled. Claims 29-51 and 58 have been examined and stand rejected, variously, under 35 U.S.C. §112, first paragraph and 35 U.S.C. §102. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Rejection Under 35 U.S.C. §112, First Paragraph

Claims 29-51 and 58 stand rejected under the first paragraph of §112 as lacking written description. The examiner argues that applicants are not in possession of cells comprising "naturally-occurring first DNA segments." Applicants have canceled claim 31, the only claim with such a recitation. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

III. Rejections Under 35 U.S.C. §102

A. Lorbach *et al.*

The examiner has rejected claims 29, 30, 32, 33, 36, 40, 41, 44-48 and 51 as anticipated by Lorbach *et al.* Applicants traverse.

First, applicants point out that this reference is a publication of the inventors' themselves, does not encompass any more disclosure than the priority application. Second, it was published ***after*** the priority date of the present application, though before the filing the parent PCT application. However, since the parent PCT application confers the further right of the German

priority application, the Lorbach *et al.* paper is not prior art. Applicants will be submitting a certified copy of the priority document shortly to perfect the priority claim.

B. Crouzet *et al.*

Claims 29, 30, 32, 33, 36, 38, 44-48 and 58 are rejected as anticipated by Crouzet *et al.* Applicants traverse.

Crouzet *et al.* describe a method for the excision of DNA segments to create therapeutic-gene-containing mini-circles using sequence specific recombination mediated by wild-type *lambda* integrase, wherein the DNA segment is flanked by two recombination sequences, *e.g.* attB/attP (see col. 4, l. 32-65). However, Crouzet *et al.* do not disclose recombination reactions in eukaryotic cells using a ***modified*** *lambda* integrase as now claimed. Furthermore, a recombination using attL/attR sites is not mentioned at all by Crouzet *et al.* Reconsideration and withdrawal of the rejection is respectfully requested.

C. Hartley *et al.*

Claims 29, 32-35, 42, 44, 45 and 58 stand rejected as anticipated by Hartley *et al.* Applicants traverse.

Hartley *et al.* provide the use of nucleic acids, vectors and methods for moving or exchanging segments of DNA molecules using engineered recombination sites and recombination proteins to generate chimeric DNA molecules (see abstract). As recombination proteins used therein, Hartley *et al.* describe *inter alia* the integrase originating from bacteriophage *lambda* for integrative recombination as well as for excision reactions. Furthermore, Hartley *et al.* describe three additional proteins (Xis, IHF and FIS) which are

essential cofactors for the *lambda* integrase protein in performing said recombination events (see col. 14, l. 13-43; col. 15, l. 1-4). However, Hartley *et al.* do not describe any modified or mutant forms of said integrase protein which are capable of recombination without the IHF cofactor as described in the present invention. Therefore, the present invention as now claimed, using modified forms of the *lambda* integrase protein, clearly is distinguishable from Hartley *et al.* Reconsideration and withdrawal of the rejection is respectfully requested.

IV. Rejections Under 35 U.S.C. §103

A. Hartley *et al.* and Christ & Dröge

Claims 29, 40 and 41 stand rejected over Hartley *et al.* and Christ & Dröge. The Examiner states that the skilled artisan would have modified the method taught by Hartley *et al.* by utilizing the mutant *lambda* integrases Int-h and Int-h/218 described in Christ & Dröge for their method of generating chimeric DNA. Applicants traverse.

Hartley *et al.* explicitly describe *lambda* integrase as being functionally dependent on co-operative and competitive interactions involving three additional proteins: the Xis, IHF and FIS proteins (see col. 14, l. 13-30). Hartley *et al.* do not provide an teachings regarding the preparation and/or use of mutant/modified integrase proteins displaying differing characteristics concerning co-operativity with its co-factors. Based on the statements in Hartley *et al.*, the artisan in the field would not even be aware of the advantages offered by the mutant integrases as described by Christ & Dröge. Therefore, the skilled artisan would not have combined the teachings of Christ & Dröge with the teachings of Hartley *et al.* in order to arrive at the present invention. Reconsideration and withdrawal of the rejection is respectfully requested.

B. Crouzet *et al.* and Hartley *et al.*

Claims 29, 36, 37 and 39 are rejected over the combined disclosures of Crouzet *et al.* and Hartley *et al.* Applicants traverse.

As discussed above, the subject-matter of the pending claims is now drawn to recombination reactions using ***modified*** integrase proteins. Thus, even if the skilled artisan would have contemplated combining the teachings of Crouzet *et al.* with the teachings of Hartley *et al.*, or *vice versa*, neither document gives any hint to combine the technical feature of modified integrase proteins. Thus, the subject-matter set forth in the present claims is in no way rendered obvious in the light of Crouzet *et al.* and Hartley *et al.* Reconsideration and withdrawal of the rejection is respectfully requested.

C. Crouzet *et a.* and Capecchi *et al.*

Claims 29 and 43 are rejected over Crouzet *et al.* and Capecchi *et al.* Applicants traverse.

As discussed above, Crouzet *et al.* describe a method for the excision of DNA segments to create therapeutic-gene-containing mini-circles using sequence specific recombination mediated by wild-type *lambda* integrase, wherein the DNA segment is flanked by two recombination sequences, *e.g.* attB/attP (see col. 4, l. 32-65). However, Crouzet *et al.* do not disclose recombination reactions in eukaryotic cells using a ***modified*** *lambda* integrase as now claimed. Furthermore, a recombination using attL/attR sites is not mentioned at all by Crouzet *et al.*

Capecchi *et al.* describe positive-negative selector vectors which are useful in the selection of transformed host cells. These vectors are inserted in the host cell by means of

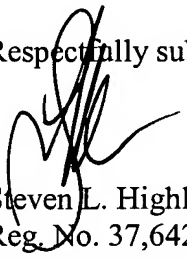
homologous recombination reactions between DNA sequences residing endogenously within the genome of a cell/organism and respective DNA sequences contained in the positive-negative selector vectors (see abstract and figure; col. 6, l. 50 to col. 7, l. 16). The method described by Capecchi *et al.* does not relate to the problem of sequence specific homologous recombination events using *lambda* integrase and *lambda* integrase specific binding/recombination sites. Accordingly, Capecchi *et al.* relate to a completely different problem and do not provide the slightest hint in regard to the present problem solved by the present invention. Moreover, as with Crouzet *et al.*, there is not mention of ***modified*** integrases. Thus, the *prima facie* case is lacking for a second reason.

Consequently, the skilled artisan would never have taken into account the teachings of Capecchi *et al.* in order to combine it with any of the technical features described therein with the teachings of Crouzet *et al.*, and even if they did, the rejection would still be defective as missing a recited element of the claims. Reconsideration and withdrawal of the rejection is respectfully requested.

V. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to the effect is earnestly solicited. Should the examiner have any questions regarding the content of this response, a telephone call to the undersigned is invited.

Respectfully submitted,



Steven L. Highlander
Reg. No. 37,642
Attorney for Peter Droge,
Nicole Christ and Elke Lorbach

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 536-3184

Date: November 23, 2004